CASE AUTH/3772/6/23

COMPLAINANT v DAIICHI SANKYO

Email promotion of Nustendi

CASE SUMMARY

This case was in relation to claims within a Nustendi (bempedoic acid, ezetimibe) promotional email.

The outcome under the 2021 Code was:

Breach of Clause 5.1	**Failing to maintain high standards**
Breach of Clause 6.1	**Making a misleading claim**
Breach of Clause 6.2	**Making an unsubstantiated claim**

No Breach of Clause 2	**Requirement that activities or materials must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**
No Breach of Clause 6.1 (x2)	**Requirement that claims/information/comparisons must not be misleading**
No Breach of Clause 6.2	**Requirement that claims/information/comparisons must be capable of substantiation**

This summary is not intended to be read in isolation.
For full details, please see the full case report below.

FULL CASE REPORT

A contactable complainant complained about an email received from a third-party publisher, which contained promotional material from Daiichi Sankyo UK Ltd.

COMPLAINT

The complaint wording is reproduced below with typographical errors corrected:

> "The claim is "NUSTENDI® (bempedoic acid + ezetimibe) is an oral option that helps to deliver additional LDL-C reduction without increasing pill burden"
>
> Below is the percent reduction that is given which is not switching from Ezetimibe, but is against placebo. It is also not against placebo from baseline, but has used "placebo corrected". Finally, this has a relative improvement rather than an absolute improvement.

The study that this was taken from has data from Ezetimibe alone as a comparator, where the drop was a much lower 23%.

With the numbers that are used makes the advert misleading, along with failing to have the absolute numbers present."

When writing to Daiichi Sankyo, the Authority asked it to consider the requirements of Clauses 2, 5.1, 6.1 and 6.2 of the 2021 Code.

DAIICHI SANKYO'S RESPONSE

The response from Daiichi Sankyo is reproduced below:

"Daiichi Sankyo UK (DSUK) takes its obligations under the ABPI Code of Practice seriously, strives to maintain high standards and always behave responsibly and ethically and we are disappointed to receive this complaint.

This letter is the DSUK formal response to the alleged breaches.

Complainant allegation 1

The complainant is concerned that a promotional email for Nustendi (BAE/23/0011) is misleading in that it refers to switching from ezetimibe to Nustendi but provides a percentage reduction of LDL- cholesterol (LDL-C) for Nustendi that is from baseline (vs placebo).

Daiichi Sankyo response 1

Nustendi is a fixed-dose combination product which contains 180mg of bempedoic acid combined with 10mg of ezetimibe. The indication for Nustendi is:

- Treatment in adults of primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet [emphasis added]:
  - in combination with a statin in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin **in addition to ezetimibe** (see sections 4.2, 4.3, and 4.4),
  - alone in patients who are either statin-intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals **with ezetimibe alone**,
  - in patients already being treated with the combination of bempedoic acid **and ezetimibe** as separate tablets with or without statin.

The intention of the promotional email as detailed in the metadata for the job bag, was to raise awareness of Nustendi. The marketing authorisation for the medicine states that a patient must already be on ezetimibe, therefore promotional material which refers to switching patients from ezetimibe to Nustendi encourages the rational use of the medicine in line with the licensed indication.

The purpose of the communication was to:

- Encourage prescribers to identify patients who may be suitable for Nustendi
- List key characteristics of the medicine
- Then provide efficacy data for Nustendi from the pivotal trial

With this in mind, the email in question initially focuses on initiating Nustendi in suitable patients, in particular by switching patients from ezetimibe without increasing the pill burden for the patient, hence the initial claim "*Switch ezetimibe to Nustendi to take back control of elevated LDL-C*".

The email then goes on to discuss the efficacy of Nustendi, with the prominent statement "*Nustendi (bempedoic acid + ezetimibe) is an oral option that helps to deliver additional LDL-C reduction without increasing pill burden*". This clearly states what Nustendi is; a combination therapy of bempedoic acid and ezetimibe.

Directly below this is a visual of a downward arrow and the claim "*Nustendi delivered a significant 38% LDL-C reduction (placebo-corrected) to help patients reach their LDL-C goals*" which communicates the efficacy results for bempedoic acid + ezetimibe as a fixed-dose combination when compared with placebo.

This figure is referenced to Ballantyne *et al* which, to date, is the only Phase 3 randomised trial that has evaluated the efficacy and safety of bempedoic acid + ezetimibe as a fixed-dose combination (i.e., the two drugs taken as a single tablet – equivalent to Nustendi) in patients receiving a maximally tolerated statin therapy. The primary efficacy endpoint was the percentage change from baseline to week 12 in LDL-C. At week 12, the LDL-C reduction seen with bempedoic acid + ezetimibe as a fixed-dose combination was significantly greater than that for the placebo group (-36.2% versus 1.8%), ($P<0.001$) with a placebo corrected reduction of 38%.

In the email at issue, reference to a 38% reduction appears immediately below the claim "*Nustendi (bempedoic acid + ezetimibe) is an oral option that helps to deliver additional LDL-C reduction without increasing pill burden*" and clearly states that this figure relates to a reduction vs placebo; equally it is clearly stated that this is a placebo corrected figure. We therefore do not consider that this is misleading or incapable of substantiation as alleged and we deny any breach of Clauses 6.1, 6.2, 5.1 and 2 in that regard.

Complainant allegation 2

The complainant appears concerned that the figure quoted for the LDL-C reduction seen with Nustendi in the email at issue (38%) is a relative reduction rather than an absolute reduction.

Daiichi Sankyo response 2

As noted above, the percentage reduction of LDL-C quoted in the email at issue (38%) is taken from the trial detailed in Ballantyne *et al*. For context, this study was not measuring the risk reduction in cardiovascular events seen with a bempedoic acid + ezetimibe fixed-dose combination, it was evaluating the LDL-C changes in patients compared to baseline.

This reduction was a continuous variable throughout the study, rather than the study being event driven for which the calculation of absolute risk and relative risk would be appropriate.

In the case of studies where a continuous variable such as LDL-C is being measured, there is, therefore, no risk reduction to calculate since there was no "risk event" being recorded. The figure of 38% referred to by the complainant is not a relative risk reduction but instead a percentage change reduction in LDL-C from baseline to week 12 (placebo corrected) observed in the study.

With this in mind, we do not consider that the supplementary information to Clause 6.1 is relevant, and we deny a breach in that regard. It therefore follows that we deny any breach of Clauses 5.1 and 2."

PANEL RULING

The complaint concerned a Nustendi (bempedoic acid, ezetimibe) promotional email sent by a third-party publisher titled 'Do you need a helping hand lowering elevated LDL-C [low-density lipoprotein cholesterol]? (Daiichi Sankyo product information)'.

The body of the email contained a number of claims including the prominent claim 'Switch ezetimibe to Nustendi to take back control of elevated LDL-C' beneath which it stated 'Nustendi (bempedoic acid + ezetimibe) is an oral option that helps to deliver additional LDL-C reduction without increasing pill burden'. Below this was a large downward arrow and the claim at issue, 'Nustendi delivered a significant **38% LDL-C reduction** (placebo-corrected) to help patients reach their LDL-C goals'. The claim was referenced to Ballantyne *et al* (2020) and had a dagger symbol which led to the footnote 'Placebo-corrected LDL-C reductions from baseline at 12 weeks: 38.0%, n=108. p<0.001 for Nustendi vs. placebo. Study 053 included patients with ASCVD [atherosclerotic cardiovascular disease], HeFH [heterozygous familial hypercholersterolaemia] or multiple CVD [cardiovascular disease] factors taking maximally-tolerated statin therapy (which could be no statin).'

The Panel noted that Ballantyne *et al* (2020) evaluated bempedoic acid 180 mg plus ezetimibe 10 mg fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. In this Phase 3 study, patients were randomly assigned (2:2:2:1) to treatment with the fixed-dose combination, bempedoic acid 180 mg, ezetimibe 10 mg or placebo added to stable background statin therapy for 12 weeks. The primary efficacy endpoint was the percentage change from baseline to week 12 in LDL-C. The three comparisons between the fixed dose combination and the other treatment arms (vs. placebo, vs. ezetimibe, and vs. bempedoic acid) were co-primary endpoints. The study authors reported that at week 12, the fixed-dose combination lowered LDL-C (–36.2%) significantly more than placebo (1.8% (placebo-corrected difference –38.0%); P<0.001), ezetimibe alone (–23.2%; P<0.001) or bempedoic acid alone (–17.2%; P<0.001).

The Panel understood the complainant's allegation to be that the claim 'Nustendi delivered a significant 38% LDL-C reduction (placebo-corrected) to help patients reach their LDL-C goals' was misleading because: 1) it used data comparing bempedoic acid/ezetimibe with placebo rather than comparing bempedoic acid/ezetimibe with the ezetimibe arm of the trial where the difference between the groups was less 2) it used a placebo-corrected value rather than citing

the LDL-C reduction from baseline, and 3) it gave a 'relative improvement' rather than an 'absolute improvement' and failed to provide the 'absolute numbers'.

The Panel addressed each allegation in turn.

1. **Comparison with placebo rather than ezetimibe**

The Panel noted Daiichi Sankyo's submission that the marketing authorisation for Nustendi stated that a patient must already be on ezetimibe. Ballantyne *et al* (2020) reported that at week 12, Nustendi lowered LDL-C (–36.2%) significantly more than placebo (1.8% (placebo-corrected difference –38.0%); P < 0.001), ezetimibe alone (–23.2%; P < 0.001) or bempedoic acid alone (–17.2%; P < 0.001).

The Panel took account of the content and layout of the promotional email.

In the Panel's view, the focus of the email was about switching patients from ezetimibe to Nustendi, noting the prominent claim in capital bold letters 'Switch ezetimibe to Nustendi to take back control of elevated LDL-C'. This impression was amplified by use of the statement 'additional LDL-C reduction without increasing pill burden' in the claim beneath, which stated 'Nustendi (bempedoic acid + ezetimibe) is an oral option that helps to deliver additional LDL-C reduction without increasing pill burden'.

Below this was a large downward arrow and the claim at issue, 'Nustendi delivered a significant **38% LDL-C reduction** (placebo-corrected) to help patients reach their LDL-C goals'.

The Panel noted that Nustendi versus ezetimibe was a co-primary endpoint in Ballantyne *et al*. Noting the focus of the promotional email was switching from ezetimibe to Nustendi, the Panel considered that health professionals would have expected to see results for the difference in LDL-C reduction from baseline between Nustendi and the ezetimibe arm.

The Panel noted from Ballantyne *et al* that the difference in LDL-C reduction from baseline between Nustendi and the ezetimibe arm was 13.1%, which was less than the figure of 38% provided in the promotional email that corresponded to the placebo corrected difference between Nustendi and the placebo arm.

The Panel considered that the footnote to the claim, 'Placebo-corrected LDL-C reductions from baseline at 12 weeks: 38.0%, n=108. p<0.001 for Nustendi vs. placebo' was not in the same visual field as the claim it related to and could be easily missed by a busy health professional.

The Panel considered the immediate and overall impression of the email. The Panel considered that the prominent boldened claim **'Switch ezetimibe to Nustendi to take back control of elevated LDL-C'** above reference to **'38% LDL-C reduction'**, which was also in bold font, might imply to a busy health professional that the figure related to the difference between Nustendi and ezetimibe, which was not so. Reference to 'placebo-corrected' in brackets, in a less prominent font, and the associated footnote, which was not in the same visual field as the claim, did not negate this misleading impression and the Panel therefore ruled **a breach of Clause 6.1**. The Panel considered that the misleading impression given that '38% LDL-C reduction' was the difference between Nustendi and ezetimibe was incapable of substantiation and ruled **a breach of Clause 6.2**.

2. Use of a placebo-corrected value

The complainant alleged, 'It is also not against placebo from baseline, but has used "placebo corrected"'.

The Panel understood the complainant's allegation to be narrow in that the claim 'Nustendi delivered a significant 38% LDL-C reduction (placebo-corrected) to help patients reach their LDL-C goals' used a placebo-corrected value rather than citing the LDL-C reduction from baseline.

The Panel noted that Ballantyne *et al* (2020) stated that at week 12, Nustendi lowered LDL-C (–36.2%) significantly more than placebo (1.8% (placebo-corrected difference –38.0%); P<0.001). The Panel further noted that Section 5.1 of the Nustendi summary of product characteristics referred to this study and stated, 'Nustendi significantly reduced LDL-C from baseline to week 12 compared with placebo (-38.0%; 95% CI: -46.5%,-29.6%; p < 0.001).

The Panel considered that the complainant had not established that using the placebo-corrected difference was misleading or incapable of substantiation and the Panel ruled **no breach of Clauses 6.1 and 6.2** on the narrow ground alleged**.**

3. Relative vs absolute

The complainant alleged that the email referred to relative improvement rather than absolute improvement and failed to have the absolute numbers present.

The Panel noted that the supplementary information to Clause 6.1 included that referring only to relative risk, especially with regard to risk reduction, can make a medicine appear more effective than it actually is. In order to assess the clinical impact of an outcome, the reader also needs to know the absolute risk involved. In that regard, relative risk should never be referred to without also referring to the absolute risk. Absolute risk can be referred to in isolation.

Daiichi Sankyo submitted that Ballantyne *et al* (2020) was not measuring the risk reduction in cardiovascular events seen with the fixed-dose combination, rather it was evaluating the LDL-C changes in patients compared to baseline. According to Daiichi Sankyo, this reduction was a continuous variable throughout the study and the figure of 38% referred to by the complainant was not a relative risk reduction but instead a percentage change reduction in LDL-C from baseline to week 12 (placebo corrected) observed in the study.

While in the Panel's view it may have been helpful for the material to provide additional detail about the study, including mean baseline LDL-C levels, the Panel considered that the figure of 38% in the claim 'Nustendi delivered a significant 38% LDL-C reduction (placebo-corrected) to help patients reach their LDL-C goals' was a placebo-corrected percentage reduction from baseline and not a relative risk reduction as referred to in the supplementary information to Clause 6.1. In that regard, the Panel ruled **no breach of Clause 6.1**.

Overall

The Panel noted its rulings of breaches of the Code at Point 1 above. The Panel considered that presenting the difference in LDL-C percent change from baseline between Nustendi and placebo was not necessarily unacceptable, however, it must not be presented in a way that

could imply it related to a different treatment comparison. The context and layout of the material was important in this regard. It was fundamental that health professionals could rely on companies to provide information about their medicines that was unambiguous.

The Panel considered that the misleading impression given in the promotional email that the figure of 38% LDL-C reduction related to the difference between Nustendi and ezetimibe, which was not so, was such that Daiichi Sankyo had failed to maintain high standards and **a breach of Clause 5.1** was ruled.

The Panel did not consider that the matter warranted a breach of Clause 2, which was a sign of particular censure and reserved for such use. The Panel therefore ruled **no breach of Clause 2**.

Complaint received **1 June 2023**

Case completed **25 July 2024**